HED DOC. NO. 013435

DATE: June 2, 1999

MEMORANDUM

SUBJECT: ***TRICHLORFON*** **- REPLACEMENT OF HUMAN STUDY USED IN RISK ASSESSMENTS -** Report of the Hazard Identification Assessment Review Committee.

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and
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On February 11, 1999, the Health Effect Division's (HED) Hazard Identification Assessment Review Committee (HIARC) reviewed the toxicology database for trichlorfon and selected doses and toxicology endpoints for risk assessment, based solely on **animal toxicity studies**. The HIARC also determined the appropriate uncertainty factors and margins of exposures for dietary and non-dietary risk assessments. **For clarity, transparency, and utility, the decisions made at the previous HIARC meetings along with those made at this meeting are presented in this report. Consequently, the information contained in this report should be used for risk**

assessments and supersedes all other reports (RfD, TES, HIARC, etc) for trichlorfon.

Committee Members in Attendance

Members present were: David Anderson, William Burnam, Virginia Dobozy, Pam Hurley, Mike Ioannou, Tina Levine, Susan Makris, Nicole Paquette, Kathleen Raffaele, Jess Rowland, Brenda Tarplee (Executive Secretary), and Pauline Wagner. Member in absentia: Karen Hamernik.

Other HED staff present at the meeting were: George Ghali, Ray Kent, Abdallah Khasawinah**.**

Brenda Tarplee
Executive Secretary
Hazard Identification Assessment Review Committee

I. BACKGROUND

Trichlorfon was reviewed by HED's Toxicology Endpoint Selection Committee for selection of doses and endpoints for dietary and non-dietary risk assessments (TES Documents dated 3/28/94 and 2/16/95). The Hazard Identification Assessment Review Committee (HIARC) evaluated the toxicology database to address the increased susceptibility of infants and children as required by the Food Quality Protection Act of 1996 (HIARC Report dated October 8, 1997).

In December 10-11, 1998, the Science Advisory Board/Scientific Advisory Panel discussed both the ethical concerns and the scientific merit of using humans subjects for testing pesticides. The Agency is currently developing a policy for the use of human studies in risk assessment. In the interim, HED has taken the following course of action.

In January, 1999, the HIARC developed a specific outline of parameters and questions for the re-examination of human studies. Human studies were used in endpoint selection for risk assessment for eight organophosphates, including trichlorfon. These studies were re-evaluated according to the parameters and questions developed by the Committee. The HIARC then selected doses and endpoints from toxicity studies with animals for each of these eight organophosphate. The HIARC examined the human data in conjunction with the animal data to determine the appropriate inter-species uncertainty factor.

In the evaluation of the comparative toxicology data in laboratory animals and humans, the Committee relied mainly on the LOAEL for cholinesterase inhibition at comparable time points (duration). The comparative data were evaluated as follows:

> If the comparative data indicate (by the dose level and the magnitude of the effect) that humans are more sensitive than laboratory animals, there is no justification for reducing the 10x inter-species uncertainty factor.
>
> If the comparative data indicate (by the dose level and the magnitude of the effect) that humans and laboratory animals are equally sensitive or that humans are less sensitive than laboratory animals, consideration was given to reducing the inter-species uncertainty factor.

On January 27, 1999, using the parameters developed for evaluation of the human studies, the HIARC evaluated the clinical trial conducted with trichlorfon on Alzheimer's patients (Becker et al., 1990MRID No. 443080-01). The HIARC classified this study as *supplemental* because the purpose of this study was to produce an effect level for the treatment of Alzheimer’s Disease and therefore the results are not appropriate for risk assessments to the general population.

On February 18, 1999, HIARC evaluated the doses and toxicology endpoints selected for

trichlorfon based solely on animal toxicity studies The HIARC also determined the appropriate uncertainty factors and margins of exposures for dietary and non-dietary risk assessments.

For clarity, transparency, and utility, the decisions made at the previous HIARC meetings along with those made at this meeting are presented in this report. Consequently, the information contained in this report should be used for risk assessments.

II. HAZARD IDENTIFICATION

A. Acute Dietary Reference Dose (RfD)

Study Selected: Acute Neurotoxicity Study in the Rat §81-8

MRID No. 4457801

Executive Summary: In an acute neurotoxicity study, groups of Fischer 344 rats (18/sex/dose) received a single oral administration of trichlorfon in deionized water at 0, 10, 50 or 200 mg/kg. Assessments were made for Functional Observation Battery (FOB) and motor activity and cholinesterase (plasma, red blood cell and brain) activity. was measured at the same intervals. The NOAEL was 10 mg/kg and the LOAEL was 50 mg/kg based on clinical signs (oral stains, red nasal stains, urine stains), alterations in FOB, decreased motor activity, and significant plasma, RBC and brain cholinesterase inhibition at 50 mg/kg (LOAEL).

Dose and Endpoint for Risk Assessment: NOAEL=10 mg/kg based on clinical, alterations in FOB, decreased motor activity and inhibition of plasma, RBC and brain cholinesterase activity in both sexes at 50 mg/kg (LOAEL).

Uncertainty Factor: 100 (10x for intra-species variation and 10x for inter-species extrapolation).

~~**Acute RfD** = 10 mg/kg/day (LOAEL) = **0.01 mg/kg**~~
~~100 (UF)~~ Revised 07/28/99 BSTarplee

Acute RfD = 10 mg/kg/day (NOAEL) = **0.10 mg/kg**
100 (UF)

Comments about study, endpoint and UF: **This dose and endpoint replaces the previous dose/endpoint based on the human study.** The dose/endpoint/study is appropriate for this risk assessment because the effects were seen after a single exposure.

The HIARC concluded that the 10x inter-species factor cannot be modified/altered. The study in humans (Becker *et al.* 1990) is useful only as *supplemental* data. This

study is a clinical trial conducted in Alzheimer's patients (compromised test subjects) and although the effects (intended to be achieved in these patients) were seen at day 7 (70% plasma and 15% RBC cholinesterase inhibition) after a single dose (2.5 mg/kg/day), they are not suitable for extrapolation to the general population and thus not appropriate for risk assessment Therefore, no comparison of dose and effects in humans and animals could be made.

B. Chronic Dietary RfD

Study: Chronic Feeding/Carcinogenicity-Monkeys §83-1b

MRID No. 40776001

Executive Summary: In a ten year chronic feeding/ oncogenicity study in Rhesus monkeys, trichlorfon was administered in Tang orange juice to male and female Rhesus monkeys at dose levels of 0, 0.2, 1.0 or 5.0 mg/kg. The NOAEL was 0.2 mg/kg/day based on inhibition of brain cholinesterase activity at 1.0 mg/kg/day (LOAEL)..

Dose and Endpoint for Risk Assessment: NOAEL=0.2 mg/kg based on brain cholinesterase inhibition in males and females at 1.0 mg/kg/day.

Uncertainty Factor: 100 (10x for intra-species variation and 10x for inter-species extrapolation).

$$\textbf{Chronic RfD} = \frac{\text{0.2 mg/kg/day (NOAEL)}}{\text{100 (UF)}} = \textbf{0.002 mg/kg/day}$$

Comments about study, endpoint and UF: **No change from the previous dose/endpoint selected based on the monkey study cited above (i.e., human data was not used previously).** The UF includes the 10x for inter-species extrapolation and 10x for intra-species variation

The HIARC concluded that the 10x inter-species extrapolation factor cannot be modified/altered. The study in humans (Becker *et al.* 1990) is useful only as *supplemental* data. This study is a clinical trial conducted in Alzheimer's patients (compromised test subjects) and is not appropriate for use in risk assessments for the general population.

C. Occupational/Residential Exposure

1. Dermal Absorption

A dermal absorption factor is required since oral value was selected for Long-Term dermal risk assessment. The Committee extrapolated a 10% dermal absorption value for trichlorfon. This extrapolation was based upon the comparisons of LOAELs in the oral developmental toxicity (LOAEL = 35 mg/kg/day) and the 21-day dermal toxicity (LOAEL = 300 mg/kg/day) in rabbits. (*Memorandum:* J. Rowland dated July 7, 1998).

Dermal Absorption Factor: 10% (extrapolated)

2. Short-Term Dermal (1-7 days)

Study Selected: 21-Day Dermal Toxicity-Rabbit §82-2

MRID No. 00403069

Executive Summary: In a 21 day dermal toxicity study, trichlorfon was administered to New Zealand White rabbits (5 days /week for 3 weeks) at doses of 0, 100, 300 or 1000 mg/kg/day. The systemic NOAEL was greater than the highest dose tested. The NOAEL for cholinesterase inhibition was 100 mg/kg/day and the LOAEL was 300 mg/kg/day based on significant depression in red blood cell cholinesterase activity.

Dose and Endpoint for Risk Assessment: NOAEL=100 mg/kg based on significant inhibition of red blood cell cholinesterase activity at 300 mg/kg/day (LOAEL).

Comments about Study/Endpoint: **No change from the previous dose/endpoint selected based on the dermal study in rabbit s cited above (i.e., human data was not used previously).**

This risk assessment is required.

3. Intermediate-Term Dermal (7 Days to Several Months)

Study Selected: 21-Day Dermal Toxicity-Rabbit §82-2

MRID No. 00403069

Executive Summary: See Short-Term Dermal

Dose and Endpoint for Risk Assessment: NOAEL=100 mg/kg based on significant inhibition of red blood cell cholinesterase activity at 300 mg/kg/day (LOAEL).

Comments about Study/Endpoint: **No change from the previous dose/endpoint selected based on the dermal study in rabbit s cited above (i.e., human data was not used previously).**

This risk assessment is required.

4. Long-Term Dermal (Several Months to Life-Time)

Study: Chronic Feeding/Carcinogenicity-Monkeys §83-1b

MRID No. 40776001

Executive Summary: See Chronic Dietary.

Dose and Endpoint for Risk Assessment: NOAEL=0.2 mg/kg based on brain cholinesterase inhibition in males and females at 1.0 mg/kg/day.

Comments about Study/Endpoint: The TES Committee did not select a dose and endpoint for this risk assessment. This risk assessment is required if there is potential long-term exposure concern.

Since an oral value was selected 10% dermal absorption factor must be used in route-to-route extrapolation for this dermal risk assessment.

This risk assessment is required.

5. Inhalation Exposure (Any Time period)

Study Selected: 21-Day Inhalation Toxicity-Rat §82-4

MRID No. 00256446

Executive Summary: Groups of SPF Wistar II rats (10/sex/concentration) were exposed to aerosol of Trichlorfon at concentrations averaging 12.7,

35.4 or 103.5 mg/m^3, 6 hours/day during a 3 week period (total exposures = 15). As measured by a cascade impactor, 93% of the droplets were 1.0±0.5µM in diameter (the remainder, <5.0µM). A control group (10/sex) were exposed to ethanol-polyethyleneglycol solvent at 20 mL/m^3. Clinical observations were recorded daily, body weights were determined weekly, and clinical pathology (hematology, clinical chemistry and urinalysis) was assessed 24 hours after last exposure. Plasma and red blood cell cholinesterase activity was measured in one-half of each group after the 5th, 10th, and 15th exposure and brain cholinesterase activity was measure at necropsy.

Except for an accidental death in one female at the mid dose, no mortality occurred at any group. Treatment had no adverse effect on body weight or body weight gain. No treatment-related effects were observed in any of the hematology, clinical chemistry or urinalysis parameters. Both sexes of rats at the mid- (35.4 mg/$m^{3)}$ and high dose (103.5 mg/m^3) groups exhibited decreases in plasma (25 to 47%), red blood cell (25 to 30%), and brain (22 to 47%) cholinesterase activity with the inhibition being more sever in the females. Histopathological examination did not reveal and treatment-related changes. Respiratory tract alterations (tracheal inflammatory cell infiltrations and mucus, pulmonary cell infiltrations and emphysema) seen in all treated rats were similar to those seen in control animals. The NOAEL was 12.7 mg/m^3 and the LOAEL was 35.4 mg/m^3.

Dose and Endpoint for Risk Assessment: NOAEL= 0.0127 mg/L based on inhibition of .plasma, red blood cell and brain cholinesterase activity at 0.0354 mg/L

Comments about Study/Endpoint: Since this was the only inhalation toxicity study available (other than the acute LC50 study), the NOAEL identified here should be used for risk assessments for any time period (i.e., short, intermediate and long-term).

This risk assessment is required.

D. Margin of Exposure for Occupational/Exposures

A Margin of Exposure (MOE) of 100 is adequate for occupational exposure. ~~There are no registered residential uses at the present time.~~ A Margin of Exposure (MOE) of 1000 is required for residential exposure. Revised 07/28/99 BSTarplee

E. Aggregate Exposure (Food + Water + Residential) Risk Assessments

~~Since there are no registered residential uses, aggregate exposure risk assessments will be limited to food plus water.~~

For **acute** aggregate exposure risk assessment, combine the **high end** exposure values from food plus water and compare it to the acute RfD.

For **chronic** aggregate exposure risk assessment, combine the **average** exposure values from food plus water and compare it to the chronic RfD.

For short-, intermediate-, and long-term exposure, the MOEs can be combined since there is a common toxicological endpoint (i.e., cholinesterase inhibition). Revised 07/28/99 BSTarplee

$$\frac{1}{\frac{1}{MOE_{Oral}} + \frac{1}{MOE_{Dermal}} + \frac{1}{MOE_{Inhalation}}}$$

III. FQPA ASSESSMENT

The FQPA Safety Factor Committee met on June 15 and 16, 1998 to evaluate the hazard and exposure data for trichlorfon and recommend application of the FQPA Safety Factor (as required by Food Quality Protection Act of August 3, 1996), to ensure the protection of infants and children from exposure to these pesticides.

The FQPA Safety Factor Committee has determined that the 10x FQPA safety factor is required for the protection of infants and children from acute and chronic dietary exposure to trichlorfon. For details, refer to the FQPA Safety Committee Report dated August 6, 1998.

IV. ACUTE TOXICITY

Guideline No.	Study Type	MRID No.	RESULT	TOXICITY CATEGORY
81-1	Acute Oral	00256446	LD_{50} =1136 - 173 mg/kg	II
81-2	Acute Dermal	00090786	LD_{50}> 2 g/kg	II
81-3	Acute Inhalation	00256446	LC_{50} =533 mg/m^3 - 4 hours	III
81-4	Primary Eye Irritation	41571302	moderately irritating	III
81-5	Primary Dermal Irritation	40306901	moderate contact allergen	IV
81-6	Skin Sensitization	00257599	Moderate contact allergen	NA-

V. SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

The doses and toxicological endpoints selected and Margins of Exposures for various exposure scenarios are summarized below.

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY	MOE
Acute Dietary	NOAEL=10 UF = 100	Clinical signs, plasma, RBC and brain cholinesterase inhibition	Acute Neurotoxicity-Rat Study	Not Relevant
	Acute RfD =0.1 mg/kg/day			
Chronic Dietary	NOAEL=0.2 UF= 100	Brain cholinesterase inhibition in both sexes	Chronic Toxicity-Monkeys	Not Relevant
	Chronic RfD =0.002 mg/kg/day			
Dermal Absorption	Estimated based upon the comparisons of LOAELs in the oral developmental toxicity (35 mg/kg/day) and the 21-day dermal toxicity (300 mg/kg/day) in rabbits.			
Short-Term (Dermal)	Dermal NOAEL=100	Red blood cell cholinesterase inhibition	21 Day Dermal - Rabbit	100
Intermediate-Term (Dermal)	Dermal NOAEL=100	Red blood cell cholinesterase inhibition	21 Day Dermal - Rabbit	100
Long-Term (Dermal)[a]	Oral NOAEL=0.2	Brain cholinesterase inhibition in both sexes	Chronic Toxicity-Monkeys	100
Inhalation (Any Time Period)	Inhalation NOAEL= 0.0127 mg/L	Plasma, red blood cell, and brain cholinesterase inhibition	21-Day Inhalation-Rat	100

[a] = Since an oral value was selected, a 10% dermal absorption factor should be used for route to route extrapolation.

MOEs are for occupational exposure risk assessments; there are no registered residential

uses at the present time.